Manganese-Catalyzed One-Pot Conversion of Nitroarenes into N-MethylarylamineS Using Methanol

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Abstract: A manganese-catalyzed one-pot conversion of nitroarenes into N-methylarylamines has been developed. This transfer hydrogenation method employs a well-defined bench stable Mn PN3 pincer precatalyst in combination with methanol as both the reductant and the C1 source. A selection of commercially available nitroarenes was converted into N-methylarylamines in synthetically useful yields.

Introduction

N-methylamines are an important structural motif that feature within a diverse array of useful compounds, including medicines, agrochemicals, dyes and surfactants.[1] More specifically, N-methylarylamines can be found within a broad range of pharmaceuticals, including Rosiglitazone, Clobazam and Osimertinib (Scheme 1A). Traditional methods for N-methylation of arylamines include the use of hazardous reagents such as methyl iodide, dimethyl sulfate and diazomethane, which typically produce a mixture of mono- and di-methylated arylamines whilst generating stoichiometric quantities of waste.[2] Reductive couplings of arylamines with carbon dioxide or formic acid can also be employed for N-methylation.[3] Alternatively, the borrowing hydrogen approach[4] enables methanol[5] to be employed as the methylating agent for the selective mono-N-methylation of anilines (Scheme 1B).[6]

Arylamines are commonly accessed via the catalytic reduction of commercially available and inexpensive nitroarenes.[7] As such, synthetic methods that enable the formation of N-methylarylamines directly from nitroarenes are valuable. In this domain, reductive catalytic approaches employing formaldehyde, formic acid or carbon dioxide in combination with silanes or hydrogen gas have been reported.[8] Alternative approaches include the photo-reductive N-methylation of aniline over Au-TiO2,[9] and the reductive C-N cross-coupling of nitroarenes and boronic acids by P(III)/P(V)=O catalysis.[10] Methanol can be employed as both the reductant and the C1 source for the reductive methylation of nitroarenes. This attractive option, which avoids the use of expensive and/or hazardous reductants, has been developed using a variety of heterogeneous catalytic systems.[11] Some of the aforementioned methods suffer from poor selectivity for mono-N-di-methylation, which somewhat diminishes the synthetic utility. Recent advances have developed homogeneous precious metal catalysis systems based on Ru[12] and Pd[13] for the selective conversion of nitroarenes to N-methylarylamines using methanol, which exhibit good selectivity for mono-N-methylation. Despite these notable advances, the use of a catalyst based upon an earth-abundant first row transition metal for this useful transformation has not previously been reported. As part of our ongoing interest in (transfer) hydrogenation chemistry,[14] herein we report the Mn-catalyzed[15] one-pot conversion of nitroarenes into N-methylarylamines using methanol (Scheme 1C).[16]

Results and Discussion

To commence our studies, the one-pot conversion of nitrobenzene 1 to N-methylaniline 2 was selected as the model system (Table 1). After extensive optimization,[17] it was found that a catalytic system composed of the well-defined bench stable[18] Mn PN3 pincer precatalyst 3 (5 mol %) introduced by Sortais and co-workers,[19] and KOH (2 equiv.) as base in MeOH ([1] = 0.5 M) with 4 Å molecular sieves at 110 °C for 16 h gave 2 in 94% NMR yield and 90% isolated yield (entry 1). No conversion occurs in the absence of the manganese precatalyst 3 or KOH (entries 2 and 3). Interestingly, it was also found that the addition of 4 Å molecular sieves was crucial for reactivity (entry 4). Although the precise role of the 4 Å molecular sieves is not known at this stage, they may promote the transformation via nitroarene activation due to their acidic properties and/or by

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sequestering water from the reaction media to perturb important equilibria (cf. Scheme 3C). Substitution of [Mn] precatalyst 3 with the alternative Mn PNP pincer precatalyst 4[20] resulted in only 14% conversion to N-methylaniline 2 (entry 5). When NaOH or K₂CO₃ were employed as the base, lower conversions to 2 was observed (entries 6 and 7). Furthermore, increasing the reaction concentration (entry 8), lowering the reaction temperature (entry 9) and reducing the precatalyst loading to 2.5 mol % (entry 10), all lowered the efficiency of the one-pot reductive methylation process.

With optimized reaction conditions in hand (Table 1, entry 1), the scope of the one-pot conversion of nitroarenes to N-methylanilines was explored (Scheme 2). Firstly, the reductive methylation procedure performs well upon scale-up, with the formation of 2 successfully carried out on a 10 mmol scale in 83% isolated yield (0.89 g of 2).[21] Methyl substitution at the 2-, 3- and 4-positions of the nitroarene was investigated (Scheme 2A). It was found that 4- and 3-methyl substitution was tolerated, giving 65% and 84% conversion to the corresponding N-methylarylamines, respectively. However, incorporation of a 2-methyl substituent within the nitroarene resulted in complete recovery of the starting material after 16 h reaction time, which could be attributed towards the increased steric shielding of the nitro functionality causing inhibition of the transfer hydrogenation step. As product 6 was formed in the highest conversion from this series, other substitution at the 3-position within the nitroarene was subsequently explored. Gratifyingly, other alkyl (3,5-(CH₃)₂ and 3-t-Bu) groups in addition to methoxy, dimethylamino, and fluoro substitution were all tolerated at the 3-position, accessing products 8-12 in synthetically useful yields. Furthermore, functional groups that can undergo (de)hydrogenation, including alcohols and alkenes, can be present within the nitroarene and are preserved within N-methylarylamines 13 and 14. Modest conversion to 14 was observed despite full consumption of the nitroarene starting material, which was attributed to some decomposition of the nitroarene substrate and/or product 14 under the reaction conditions. 1-Methoxy-4-nitrobenzene was converted to product 15 in only 6% NMR yield using the standard reaction conditions, which increased to 30% when the reaction temperature was raised to 130 °C. The mass balance in both cases was

### Table 1: Reaction Optimization

<table>
<thead>
<tr>
<th>Entry</th>
<th>Variation from “standard” conditions</th>
<th>Yield[^b] (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>none</td>
<td>94 (90)</td>
</tr>
<tr>
<td>2</td>
<td>no [Mn] precatalyst 3</td>
<td>&lt; 2</td>
</tr>
<tr>
<td>3</td>
<td>no KOH</td>
<td>&lt; 2</td>
</tr>
<tr>
<td>4</td>
<td>no 4 Å molecular sieves</td>
<td>&lt; 2</td>
</tr>
<tr>
<td>5</td>
<td>[Mn] precatalyst 4 (5 mol %) instead of 3</td>
<td>14</td>
</tr>
<tr>
<td>6</td>
<td>NaOH (2 equiv.) instead of KOH</td>
<td>83</td>
</tr>
<tr>
<td>7</td>
<td>K₂CO₃ (2 equiv.) instead of KOH</td>
<td>83</td>
</tr>
<tr>
<td>8</td>
<td>[1] = 1 M</td>
<td>33</td>
</tr>
<tr>
<td>9</td>
<td>80 °C</td>
<td>&lt; 2</td>
</tr>
<tr>
<td>10</td>
<td>[Mn] precatalyst 3 (2.5 mol %)</td>
<td>74</td>
</tr>
</tbody>
</table>

[^a]: Reactions performed in a sealed tube using 0.5 mmol of substrate and synthesis grade MeOH. [1] = 0.5 M. [b]: As determined by ¹H NMR analysis of the crude reaction mixture with 1,3,5-trimethylbenzene as the internal standard. Isolated yield given in parentheses.

Scheme 2. Substrate Scope. Reactions performed in a sealed tube using 0.5 mmol of substrate and synthesis grade MeOH. Yields as determined by ¹H NMR analysis of the crude reaction mixture with 1,3,5-trimethylbenzene as the internal standard. Isolated yield given in parentheses. [a] 10 mmol of substrate, 24 h. [b] 72 h. [c] 130 °C.
remaining starting material, which can be explained by the mesomeric effect of the methoxy group resulting in a more challenging transfer hydrogenation of the optimized reaction conditions. A variety of alternative substrates containing nitro functional groups were incompatible with the optimized reaction conditions (Scheme 2B). It was found that nitroarenes containing hydroxyl or amino functionalities were unreactive, with starting materials returned. These substrates may inhibit catalysis via coordination to Mn and/or may be too electron rich to undergo transfer hydrogenation. Nitroarenes containing various electron-withdrawing groups at the 3-position, in addition to 1-nitrohexane and β-nitrostyrene, were each found to be incompatible with this protocol, with complex reaction mixtures obtained across a range of reaction conditions explored. However, when specific nitroarenes were subjected to the optimized reaction conditions, conversion to products other than N-methylarylamines was observed (Scheme 2C). For example, 2-nitropyridine underwent transfer hydrogenation to form 2-aminopyridine 16 in 85% isolated yield. The subsequent mono-N-methylation did not proceed, presumably due to the low nucleophilicity of arylamine 16. A nitroarene containing an ethynyl substituent at the 3-position participated in an anti-Markovnikov hydromethoxylation reaction to give 80% conversion to (Z)-enol ether 17. A subsequent control experiment revealed that this transformation requires only KOH and proceeds in the absence of [Mn] precatalyst 3.[23] Finally, 1-fluoro-4-nitrobenzene participated in a nucleophilic aromatic substitution (SNAr) reaction with methanol to give 18 in 80% isolated yield. Employing ethanol as the solvent using otherwise “standard” reaction conditions, nitrobenzene was converted into aniline in 33% NMR yield with no N-ethylation observed.

A selection of further experiments were performed in order to gain insight into the mechanism of the reaction. Initially, it was found that azobenzene 19 and azoxybenzene 20 did not convert to N-methylaniline 2 when subjected to the optimized reaction conditions, which indicated that they are not productive intermediates (Scheme 3A).[12,13] Conversely, >98% conversion to 2 was observed when aniline 21 was employed as the substrate. The reaction progress was monitored for the reductive methylation of nitrobenzene 1 (Scheme 3B).[17] Product 2 was initially formed slowly, with only 7% conversion to 2 observed after 4 h, which may partly be due to the time required for activation of the [Mn] precatalyst 3 with KOH. The long induction period prompted us to explore the stability of the catalyst by monitoring the presence of carbonyl ligands using FT-IR during the course of the reaction.[24] After 6 h reaction time, absorption bands corresponding to carbonyl ligands were observed.[17] However, the formation of a heterogeneous active species cannot be excluded. Beyond 4 h, the rate of formation of 2 increased, with 58% conversion observed after 8 h. Conversion to 2 reached a maximum of 88% after 24 h, at which time no nitrobenzene 1 remained. The small quantities of aniline 21 observed (6% after 4 h and 3% after 8 h) supported a mechanism that involved an initial transfer hydrogenation followed by condensation and subsequent aldimine hydrogenation to form 2. Dihydrogen and formaldehyde were detected via sampling the headspace of the reaction vessel and the reaction mixture, respectively.[17] The reaction is selective for mono-N-methylation, with no dimethylated products observed.

When CD$_3$OD or CD$_2$OD were employed as solvents using otherwise “standard” reaction conditions, nitrobenzene 1 was fully recovered. In line with these observations, and previous related investigations,[15,16,19] a plausible reaction mechanism initiates with activation of [Mn] precatalyst 3 with KOH to form the active manganese complex (Scheme 3C). Subsequent transfer hydrogenation converts nitrobenzene 1 and methanol into aniline 21 and formaldehyde, which can undergo a condensation reaction to form N-phenylmethylamine 22. Hydrogenation of 22 with the manganese hydride provides
access to the $N$-methylated product $2$ with regeneration of the catalytically active species. $N$-Phenylmethylamine $22$ was not observed during the time course experiment, which suggests that aldime hydrogenation must occur rapidly using these reaction conditions.

Conclusions

In conclusion, we have developed a new synthetic method for the one-pot conversion of nitroarenes into $N$-methylamylamines. Mechanistic experiments suggest a transfer hydrogenation mechanism, which employed methanol to be employed as both the methylating agent and the reductant. This is the first report that employs a well-defined organometallic complex based upon an earth-abundant first row transition metal for this transformation. Ongoing studies are focused on applications of earth-abundant transition metals in synthetic organic chemistry and these results will be reported in due course.

Acknowledgements

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Keywords: transfer hydrogenation • manganese catalysis • methanol • nitroarenes • $N$-methylamines


[21] Pressure was released after 8 h, followed by heating for a further 16 h.


[23] Enol ether 17 was formed in 73% NMR yield in the absence of [Mn] precatalyst 3.

[24] We sincerely thank the reviewers for suggesting that we investigate the stability of the catalyst.
Take the direct route!: A manganese-catalyzed one-pot conversion of nitroarenes into \(N\)-methylarylamines has been developed. This transfer hydrogenation method employs a well-defined bench stable Mn PN\(_3\)P pincer precatalyst in combination with methanol as both the reductant and the C1 source. A selection of commercially available nitroarenes was converted into \(N\)-methylarylamines in synthetically useful yields.